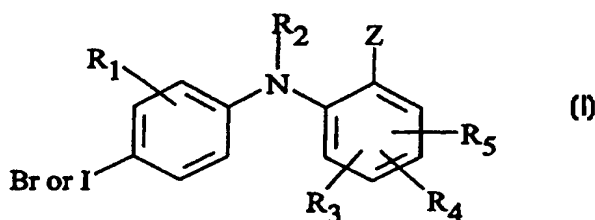




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00		A2	(11) International Publication Number: WO 00/35436
			(43) International Publication Date: 22 June 2000 (22.06.00)
(21) International Application Number: PCT/US99/29783 (22) International Filing Date: 15 December 1999 (15.12.99) (30) Priority Data: 60/112,544 16 December 1998 (16.12.98) US 60/164,651 10 November 1999 (10.11.99) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): <u>DUDLEY</u> , David, Thomas [US/US]; 3700 Waters Road, Ann Arbor, MI 48103 (US). <u>FLORY</u> , Craig, Mason [US/US]; 3448 Pineview Drive West, Dexter, MI 48130 (US). <u>SALTIEL</u> , Alan, Robert [US/US]; 2002 Valley View Drive, Ann Arbor, MI 48105 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	

(54) Title: TREATMENT OF ARTHRITIS WITH MEK INHIBITORS



(57) Abstract

This invention provides a method for preventing and treating arthritis in a mammal suffering from arthritis and in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a MEK inhibitor, including a compound of Formula (I) and Formula (II).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

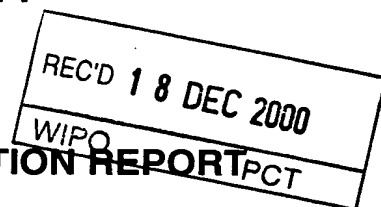
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
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BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
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CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT^{PCT}

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference PD-5968-01-EDS	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/29783	International filing date (day/month/year) 15/12/1999	Priority date (day/month/year) 16/12/1998
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 16/06/2000	Date of completion of this report 14.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Winger, R Telephone No. +49 89 2399 8129 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-81 as originally filed

Claims, No.:

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-16.

because:

- ☒ the said international application, or the said claims Nos. 1-16 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-16
	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	see section III

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/29783

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Prior Art: Reference is made to the following documents cited in the International Search Report

D1: WO 99 61440 A
D2: WO 99 57101 A
D3: WO 99 01449 A
D4: J. BIOL. CHEM., vol. 273 (1998), pages 24832-24838
D5: J. PHARM. EXP. THERAP., vol. 284 (1998), pages 687-692
D6: J. OF IMMUNOLOGY, vol. 161 (1998), pages 467-473
D7: WO 98 37881 A: cited in the application
D8: BIOORG. MED. CHEM. LETT., vol. 8 (1998), pages 3335-3340
D9: WO 98 28292 A
D10: WO 96 00082 A

3. Novelty and Inventive Step (Article 33(2) and (3) PCT):

- 3.1 Claims 1-5 relate to the treatment/prevention of arthritis comprising administering an effective antiarthritic amount of a MEK inhibitor.
Documents D4-D6 and D8-D9, which disclose imidazole and indole derivatives, respectively, acting as p38-MAPK inhibitors for the treatment of arthritis, do not seem to anticipate the subject-matter of claims 1-5.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

Document D10, however, discloses the use of bromelain, which inhibits the phosphorylation of MAPK (p 31), for the treatment of rheumatoid arthritis (claim 15), thus anticipating the subject-matter of claims 1-5, which is therefore not novel.

Besides, taking into account that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis (cf. documents D4-D6, D8-D9), the choice to inhibit the "upstream" kinase does not seem to involve an inventive step.

3.2 Claims 6-14 and 15-16 relate to the treatment/prevention of arthritis using specific MEK inhibitors/compounds.

Documents D4-D6 and D8-D9, disclose imidazole and indole derivatives, respectively, as MAPK inhibitors for the treatment of arthritis, thus differing with respect to the compounds used. Accordingly, the subject-matter of said claims seems to be novel.

The problem to be solved by the current application can be regarded as to provide alternative compounds for the treatment of arthritis.

Taking into account that document D7 discloses the same compounds as MEK inhibitors (for the treatment of septic shock) and that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis, the subject-matter of claims 6-16 does not seem to be inventive.

4. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

Re Section VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
D1: WO 99 61440 A	02.12.99	25.05.99	26.05.98
D2: WO 99 57101 A	11.11.99	28.04.99	05.05.98 and 02.03.99
D3: WO 99 01449 A	14.01.99	26.06.98	30.06.97

5. Document D1 could anticipate the novelty of claims 1-5 in the regional phase.

Re Section VII

Certain defects in the international application

6. On page 52, the name for example 207 seems to be wrong.
7. The chemical name of PD 199601 on page 77 in Table 3 seems to be missing.
8. The second concentration of PD 184352 in Table 4 on page 78 seems to be wrong.

Re Section VIII

Certain observations on the international application

9. Independent claim 1 (and dependent claims) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (MEK inhibitor) which merely amounts to a statement of the underlying problem. It is not clear which criterium (e.g., IC₅₀-test) has to be met for a compound to fall within the scope of the claim.
10. The parentheses in claim 6 for the definition of Z being hetero-cycloalkyl seem to be wrong.
11. The sulfamoyl-substituted compounds of dependent claim 7 do not seem to fall within the range of Formula I (claim 6).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

12. Claim 8 seems to be unclear ("or (k) or combinations of the above").
13. The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide in claim 13 (p 98) seems to be wrong.
14. The PD-number of the last compound in claim 14 is missing.
15. The embodiments of the invention "synthesis and synthetic intermediates" described on page 24, line 15, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
16. The embodiments of the invention "thiobenzoic acid" described on page 47, examples 140-145, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
17. The vague statement "scope" of the specification used on page 35 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret it (PCT-Guidelines, III-4.3a).

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 June 2000 (22.06.2000)

PCT

(10) International Publication Number
WO 00/35436 A3

(51) International Patent Classification⁷: A61K 31/195,
31/166, 31/136, 31/41, 31/445, 31/495, 31/535, 31/38,
31/34

Alan, Robert [US/US]; 2002 Valley View Drive, Ann Arbor, MI 48105 (US).

(21) International Application Number: PCT/US99/29783

(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

(22) International Filing Date:
15 December 1999 (15.12.1999)

(81) Designated States (*national*): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(30) Priority Data:
60/112,544 16 December 1998 (16.12.1998) US
60/164,651 10 November 1999 (10.11.1999) US

(71) Applicant (*for all designated States except US*):
WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

Published:
— with international search report

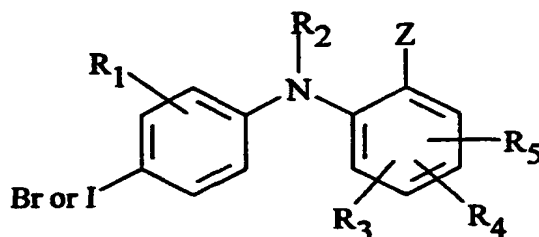
(72) Inventors; and

(88) Date of publication of the international search report:
18 October 2001

(75) Inventors/Applicants (*for US only*): DUDLEY, David, Thomas [US/US]; 3700 Waters Road, Ann Arbor, MI 48103 (US). FLORY, Craig, Mason [US/US]; 3448 Pineview Drive West, Dexter, MI 48130 (US). SALTIEL,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF ARTHRITIS WITH MEK INHIBITORS



(57) Abstract: This invention provides a method for preventing and treating arthritis in a mammal suffering from arthritis and in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a MEK inhibitor, including a compound of Formula (I) and Formula (II).

WO 00/35436 A3

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/166 A61K31/136 A61K31/41 A61K31/445
A61K31/495 A61K31/535 A61K31/38 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

	Designation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P	<p>WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8</p> <p>--- WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43</p> <p>--- WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14</p> <p>--- -/--</p>	<p>1-5</p> <p>1-5</p> <p>1-5</p>

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 April 2000

Date of mailing of the international search report

19/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

INTERNATIONAL SEARCH REPORT

Int'l. Application No
PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Y	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartilage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12, 16-19 -----	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6, 12, 14, 15, 20 page 7, line 17 -page 8, line 25 page 11, line 21 -----	1-5
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 29783

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-16
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9961440 A	02-12-1999	NONE	
WO 9957101 A	11-11-1999	NONE	
WO 9901449 A	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
WO 9837881 A	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998
WO 9828292 A	02-07-1998	NONE	
WO 9600082 A	04-01-1996	AU 2749395 A CA 2193654 A CN 1151119 A EP 0766565 A FI 965204 A JP 10502073 T NO 965564 A	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
US 5525625 A	11-06-1996	AT 181913 T AU 690400 B AU 4245696 A CA 2208075 A DE 69510696 D DE 69510696 T EP 0805807 A GR 3031295 T JP 10512878 T NZ 297320 A WO 9622985 A ZA 9600528 A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 29783	International filing date (day/month/year) 15/12/1999	(Earliest) Priority Date (day/month/year) 16/12/1998
Applicant WARNER-LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☐ None of the figures.

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 99/ 29783

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-16
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/29783

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/166 A61K31/136 A61K31/41 A61K31/445
A61K31/495 A61K31/535 A61K31/38 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 April 2000

Date of mailing of the international search report

19/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Y	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and Inducible Nitric Oxide Synthase in Bovine Cartilage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JS 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19 -----	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21 -----	1-5
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29783

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9961440	A	02-12-1999	NONE		
WO 9957101	A	11-11-1999	NONE		
WO 9901449	A	14-01-1999	AU	8801598 A	25-01-1999
			NO	996429 A	23-12-1999
			ZA	9805656 A	30-12-1998
WO 9837881	A	03-09-1998	AU	5610398 A	18-09-1998
			ZA	9801578 A	02-09-1998
WO 9828292	A	02-07-1998	NONE		
WO 9600082	A	04-01-1996	AU	2749395 A	19-01-1996
			CA	2193654 A	04-01-1996
			CN	1151119 A	04-06-1997
			EP	0766565 A	09-04-1997
			FI	965204 A	21-02-1997
			JP	10502073 T	24-02-1998
			NO	965564 A	24-02-1997
US 5525625	A	11-06-1996	AT	181913 T	15-07-1999
			AU	690400 B	23-04-1998
			AU	4245696 A	14-08-1996
			CA	2208075 A	01-08-1996
			DE	69510696 D	12-08-1999
			DE	69510696 T	23-12-1999
			EP	0805807 A	12-11-1997
			GR	3031295 T	31-12-1999
			JP	10512878 T	08-12-1998
			NZ	297320 A	28-05-1999
			WO	9622985 A	01-08-1996
			ZA	9600528 A	15-08-1996

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 29783	International filing date (day/month/year) 15/12/1999	(Earliest) Priority Date (day/month/year) 16/12/1998
Applicant WARNER-LAMBERT COMPANY et al.		

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This International Search Report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-16
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29783

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/166 A61K31/136 A61K31/41 A61K31/445
 A61K31/495 A61K31/535 A61K31/38 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8 ---	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43 ---	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14 --- -/--	1-5

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 April 2000

Date of mailing of the international search report

19/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Y	page 24837, right-hand column, last paragraph	6-16
X	--- J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	--- A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartilage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	--- WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	--- HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2 --- -/--	1-5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19 ----	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21 ----	1-5
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29783

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
W0 9961440	A	02-12-1999	NONE	
W0 9957101	A	11-11-1999	NONE	
W0 9901449	A	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
W0 9837881	A	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998
W0 9828292	A	02-07-1998	NONE	
W0 9600082	A	04-01-1996	AU 2749395 A CA 2193654 A CN 1151119 A EP 0766565 A FI 965204 A JP 10502073 T NO 965564 A	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 29783	International filing date (day/month/year) 15/12/1999	(Earliest) Priority Date (day/month/year) 16/12/1998
Applicant WARNER-LAMBERT COMPANY et al.		

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a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

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☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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2. ☒ **Certain claims were found unsearchable** (See Box I).

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5. With regard to the **abstract**,

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6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-16
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/29783

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/166 A61K31/136 A61K31/41 A61K31/445
 A61K31/495 A61K31/535 A61K31/38 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8 ---	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43 ---	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14. --- -/--	1-5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 April 2000

Date of mailing of the international search report

19/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Y	page 24837, right-hand column, last paragraph	6-16
X	--- J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	--- A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartilage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	--- WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	--- HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2 --- -/--	1-5

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12, 16-19 ----	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6, 12, 14, 15, 20 page 7, line 17 -page 8, line 25 page 11, line 21 ----	1-5
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29783

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9961440	A	02-12-1999	NONE	
WO 9957101	A	11-11-1999	NONE	
WO 9901449	A	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
WO 9837881	A	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998
WO 9828292	A	02-07-1998	NONE	
WO 9600082	A	04-01-1996	AU 2749395 A CA 2193654 A CN 1151119 A EP 0766565 A FI 965204 A JP 10502073 T NO 965564 A	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
US 5525625	A	11-06-1996	AT 181913 T AU 690400 B AU 4245696 A CA 2208075 A DE 69510696 D DE 69510696 T EP 0805807 A GR 3031295 T JP 10512878 T NZ 297320 A WO 9622985 A ZA 9600528 A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996

PCT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C. 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year)

16 August 2000 (16.08.00)

International application No.

PCT/US99/29783

Applicant's or agent's file reference

5968-01-EDS

International filing date (day/month/year)

15 December 1999 (15.12.99)

Priority date (day/month/year)

16 December 1998 (16.12.98)

Applicant

DUDLEY, David, Thomas et al

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

16 June 2000 (16.06.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Christelle Croci

Telephone No.: (41-22) 338.83.38

- Rose Armstrong
Charles AshbrookFrom the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

MANSMANN, I.
Warner-Lambert Company
Legal Division
c/o Gödecke AG, Patents
Mooswaldallee 1
D-79090 Freiburg
ALLEMAGNEPatentwesen
Eing.: 15. Dez. 2000NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)Date of mailing
(day/month/year)

14.12.2000

Applicant's or agent's file reference
PD-5968-01-EDS

IMPORTANT NOTIFICATION

International application No.
PCT/US99/29783International filing date (day/month/year)
15/12/1999Priority date (day/month/year)
16/12/1998

Applicant

WARNER-LAMBERT COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523658 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hundt, D

Tel. +49 89





PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD-5968-01-EDS		FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/29783	International filing date (day/month/year) 15/12/1999	Priority date (day/month/year) 16/12/1998	
International Patent Classification (IPC) or national classification and IPC A61K31/00			
Applicant WARNER-LAMBERT COMPANY et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input checked="" type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 16/06/2000		Date of completion of this report 14.12.2000	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Winger, R Telephone No. +49 89 2399 8129 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/29783

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-81 as originally filed

Claims, No.:

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US99/29783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-16.

because:

- ☒ the said international application, or the said claims Nos. 1-16 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 6-16
	No: Claims 1-5
Inventive step (IS)	Yes: Claims
	No: Claims 1-16
Industrial applicability (IA)	Yes: Claims see section III

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US99/29783**

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Prior Art: Reference is made to the following documents cited in the International Search Report

D1: WO 99 61440 A
D2: WO 99 57101 A
D3: WO 99 01449 A
D4: J. BIOL. CHEM., vol. 273 (1998), pages 24832-24838
D5: J. PHARM. EXP. THERAP., vol. 284 (1998), pages 687-692
D6: J. OF IMMUNOLOGY, vol. 161 (1998), pages 467-473
D7: WO 98 37881 A: cited in the application
D8: BIOORG. MED. CHEM. LETT., vol. 8 (1998), pages 3335-3340
D9: WO 98 28292 A
D10: WO 96 00082 A

3. Novelty and Inventive Step (Article 33(2) and (3) PCT):

- 3.1 Claims 1-5 relate to the treatment/prevention of arthritis comprising administering an effective antiarthritic amount of a MEK inhibitor.
Documents D4-D6 and D8-D9, which disclose imidazole and indole derivatives, respectively, acting as p38-MAPK inhibitors for the treatment of arthritis, do not seem to anticipate the subject-matter of claims 1-5.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

Document D10, however, discloses the use of bromelain, which inhibits the phosphorylation of MAPK (p 31), for the treatment of rheumatoid arthritis (claim 15), thus anticipating the subject-matter of claims 1-5, which is therefore not novel.

Besides, taking into account that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis (cf. documents D4-D6, D8-D9), the choice to inhibit the "upstream" kinase does not seem to involve an inventive step.

3.2 Claims 6-14 and 15-16 relate to the treatment/prevention of arthritis using specific MEK inhibitors/compounds.

Documents D4-D6 and D8-D9, disclose imidazole and indole derivatives, respectively, as MAPK inhibitors for the treatment of arthritis, thus differing with respect to the compounds used. Accordingly, the subject-matter of said claims seems to be novel.

The problem to be solved by the current application can be regarded as to provide alternative compounds for the treatment of arthritis.

Taking into account that document D7 discloses the same compounds as MEK inhibitors (for the treatment of septic shock) and that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis, the subject-matter of claims 6-16 does not seem to be inventive.

4. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

Re Section VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
D1: WO 99 61440 A	02.12.99	25.05.99	26.05.98
D2: WO 99 57101 A	11.11.99	28.04.99	05.05.98 and 02.03.99
D3: WO 99 01449 A	14.01.99	26.06.98	30.06.97

5. Document D1 could anticipate the novelty of claims 1-5 in the regional phase.

Re Section VII

Certain defects in the international application

6. On page 52, the name for example 207 seems to be wrong.
7. The chemical name of PD 199601 on page 77 in Table 3 seems to be missing.
8. The second concentration of PD 184352 in Table 4 on page 78 seems to be wrong.

Re Section VIII

Certain observations on the international application

9. Independent claim 1 (and dependent claims) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (MEK inhibitor) which merely amounts to a statement of the underlying problem. It is not clear which criterium (e.g., IC_{50} -test) has to be met for a compound to fall within the scope of the claim.
10. The parentheses in claim 6 for the definition of Z being hetero-cycloalkyl seem to be wrong.
11. The sulfamoyl-substituted compounds of dependent claim 7 do not seem to fall within the range of Formula I (claim 6).

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/29783

12. Claim 8 seems to be unclear ("or (k) or combinations of the above").
13. The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide in claim 13 (p 98) seems to be wrong.
14. The PD-number of the last compound in claim 14 is missing.
15. The embodiments of the invention "synthesis and synthetic intermediates" described on page 24, line 15, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
16. The embodiments of the invention "thiobenzoic acid" described on page 47, examples 140-145, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
17. The vague statement "scope" of the specification used on page 35 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret it (PCT-Guidelines, III-4.3a).

NOTED

APR 25 2000

PATENT COOPERATION TREATY

R. ARMSTRONG

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

WARNER-LAMBERT COMPANY
Attn. RYAN, M. A.
201 Tabor Road
Morris Plains, New Jersey 07950
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

APR 24 2000

(PCT Rule 44.1)

MP PATENT DEPT.

Date of mailing
(day/month/year)

19/04/2000

Applicant's or agent's file reference

5968-01-EDS

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 99/29783

International filing date

(day/month/year)

15/12/1999

Applicant

WARNER-LAMBERT COMPANY et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Renate Jordan

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46:4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 29783	International filing date (day/month/year) 15/12/1999	(Earliest) Priority Date (day/month/year) 16/12/1998
Applicant WARNER-LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-16
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-16
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29783

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/195 A61K31/166 A61K31/136 A61K31/41 A61K31/445
 A61K31/495 A61K31/535 A61K31/38 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14 -/-	1-5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 April 2000

Date of mailing of the international search report

19/04/2000

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Y	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartilage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/29783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19 ---	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21 ---	1-5
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/29783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9961440 A	02-12-1999	NONE	
WO 9957101 A	11-11-1999	NONE	
WO 9901449 A	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
WO 9837881 A	03-09-1998	AU 5610398 A ZA 9801578 A	18-09-1998 02-09-1998
WO 9828292 A	02-07-1998	NONE	
WO 9600082 A	04-01-1996	AU 2749395 A CA 2193654 A CN 1151119 A EP 0766565 A FI 965204 A JP 10502073 T NO 965564 A	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
US 5525625 A	11-06-1996	AT 181913 T AU 690400 B AU 4245696 A CA 2208075 A DE 69510696 D DE 69510696 T EP 0805807 A GR 3031295 T JP 10512878 T NZ 297320 A WO 9622985 A ZA 9600528 A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996